Tetrahedron, 1964, Vol. 20, pp. 1173 to 1177. Pergamon Press Ltd. Printed in Northern Ireland

STEREOISOMERISM OF QUATERNARY SALTS OF 5-NITROTETRAHYDRO-1,3-OXAZINES*

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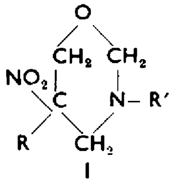
(*Received* 27 *January* 1964)

Abstract—A number of diastereoisomeric pairs of quaternary salts of tetrahydro-1,3-oxazine derivatives have been prepared by the action of n-alkyl bromide (iodide) on 5-nitrotetrahydro-1,3-oxazines. The products are substituted at N_3 by an axial n-alkyl different from that present in the n-alkyl bromide (iodide). Similar isomeric pairs with benzyl and methyl attached to N_3 were obtained.

The conformational analysis was based on former work concerning the stereochemistry of 1,3-oxazine and the present NMR investigation.

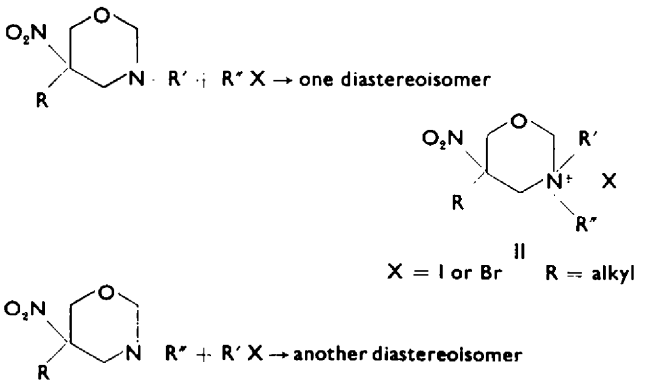
A previous study[1,2] concerning the conformation of 5-nitrotetrahydro-1,3-oxazines (I) led to the conclusion that the ring



I

(with R = alkyl) exists in the chair form with the nitro group in the axial position. The substituent (R′) at the nitrogen atom may be axial (R′ = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, benzyl) or equatorial (R′ = t-C_4H_9, cyclohexyl), as inferred from dipole moments and NMR spectra.[2] It was also found that the conformation is fixed at room temperature.

The alkylation at the nitrogen to form quaternary salts should result in either of two possible diastereoisomeric forms, depending on which of the two alkyl groups is introduced in the second place. Actually, the pairs of products obtained in the reactions for various combinations of substituents, showed differences in melting points and decided mixed melting point depressions.



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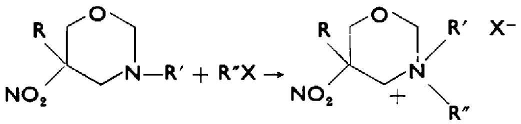
* Paper read at XIX-th International Congress of Pure and Applied Chemistry, London, July 1963 (Paper LXII of the series "Aliphatic Nitro Compounds").

[1] D. Gürne and T. Urbański, *J. Chem. Soc.* 1912 (1959).

[2] D. Gürne, T. Urbański, M. Witanowski and L. Stefaniak, *Tetrahedron*, Supl. 1964. In press.

TABLE 1



R′	R″	X	R = CH_3 m.p.	R = CH_3 mixed	R = C_2H_5 m.p.	R = C_2H_5 mixed m.p.	R = n-C_3H_7 m.p.	R = n-C_3H_7 mixed m.p.	R = n-C_4H_9 m.p.	R = n-C_4H_9 mixed m.p.	R = n-C_5H_{11} m.p.	R = n-C_5H_{11} mixed m.p.
CH_3	C_2H_5	I	163–164		185–186		189–191		148–150		125–127	
				139–144		147–150		152–155		122–125		115–117
C_2H_5	CH_3	I	161–163		149–150		159–161		143–146		158–160	
CH_3	C_2H_5	Br	183–185		180–181		166–167		—	—	—	
				163–165		175–178		134–138		—		—
C_2H_5	CH_3	Br	186–188		191–193		143–145		—		—	
CH_3	n-C_3H_7	Br	190–192		181–182		—		—		—	
				155–161		162–165		—		—		—
n-C_3H_7	CH_3	Br	165–167		184–186		—		—		—	
CH_3	n-C_4H_9	Br	164–166		161–162		210–215		—		—	
				145–149		141–144		139–144		—		—
n-C_4H_9	CH_3	Br	166–167		172–174		170–173		—		—	
CH_3	$CH_2C_6H_5$	Br	—		178–179		—		—		—	
				—		168–171		—		—		—
$CH_2C_6H_5$	CH_3	Br	—		179–180		—		—		—	

Direct proof of diastereoisomerism was afforded by NMR investigations of dilute solutions of the products in deuterium oxide. The NMR spectra of two such products are essentially the same except for small but regular differences in the chemical shifts (Fig. 1), indicating that only long-range shielding effects in different spatial arrangements are involved.

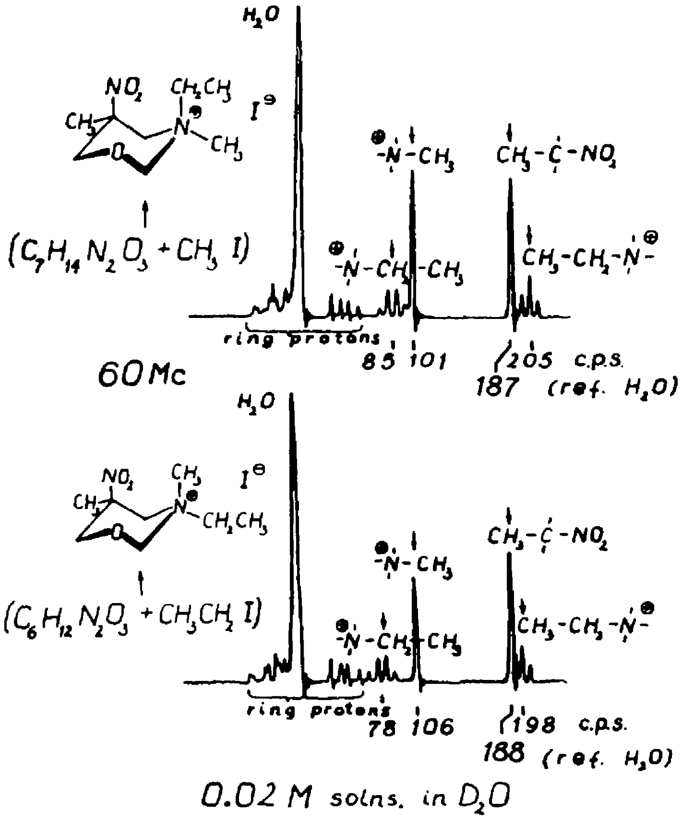


FIG. 1

The NMR signal of the alkyl introduced lies some 0·1 ppm downfields as compared with the case where the same alkyl was originally present on the nitrogen atom.

Consideration of the long-range shielding effects in the ring leads to some conclusions on the conformation of the quaternary salts. The well-known effect of the single bonds in a six-membered saturated ring in the chair conformation[2] should result in shifting the axial alkyl signal to higher fields relative to the equatorial alkyl. The nitro group is assumed to have a similar effect, based on the previous investigations[1,2] indicating the axial nitro group and suggesting that the NO_2 plane is approximately perpendicular to the C_2–C_5 axis. If the same conformation at C_5 is preserved in the quaternary salts, then the axial substituent at the nitrogen should lie in the positive shielding area (shift to higher fields), believed to extend conically above and below the NO_2 plane.[3] (Fig. 2).

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[3] L. M. Jackman, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London (1959).

Based on these assumptions, the NMR spectra of the compounds examined, suggest that the alkyl originally present in the ring is axial in the quaternary salt and the alkyl introduced is equatorial. Since all diastereoisomeric pairs were obtained from the compounds with an axial substituent at the nitrogen (R′ = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, —$CH_2C_6H_5$), the postulated course of alkylation is as follows:

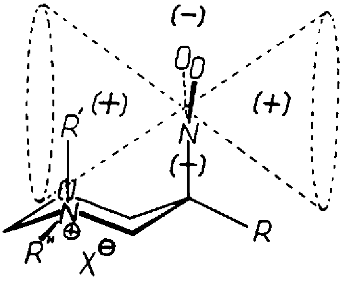
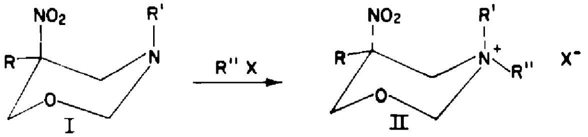


FIG. 2



I

II

R′ = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, —$CH_2C_6H_5$
R″ = CH_3, C_2H_5, n-C_3H_7, n-C_4H_9, —$CH_2C_6H_5$

i.e. the attack occurs at the equatorial position assuming that no ring conversion takes place during quaternization.

Under similar experimental conditions, attempts at quaternization of the 5-nitrotetrahydro-1,3-oxazines (I), when R′ = t-C_4H_9 or cyclohexyl both in equatorial position as shown earlier,[1,2] failed probably because of steric hindrance. The reaction with methyl bromide (I) yielded only traces of the corresponding hydrogen bromide salts.

In the analogous compound I (with axial R′ = CH_3), quaternization with t-C_4H_9 bromide yielded the elimination products and the hydrobromide of I in quantitative yield.

Quaternary salts (II) differ from 5-nitrotetrahydro-1,3-oxazines (I) in that they are not subject to ring opening with dilute hydrochloric acid[5–7] and splitting off a molecule of formaldehyde, which is typical for the compounds I.

It was formerly found that irradiation with ultraviolet light considerably increases the rate of hydrolysis and ring opening of derivatives of I. Under these conditions, quaternary salts (II) undergo complete decomposition and we were unable to isolate any definite compound from the tarry mixture.

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[4] J. Yamaguchi, *Mol. Phys.* **6**, 105 (1963).

[5] E. L. Hirst, J. K. N. Jones, S. Minahan, F. W. Ochyński, A. T. Thomas and T. Urbański, *J. Chem. Soc.* 924 (1947).

[6] Z. Eckstein, W. Sobótka and T. Urbański, *Rocz. Chem.* **30**, 132 (1956).

[7] D. Gürne and T. Urbański, *Rocz. Chem.* **31**, 855 (1957); **31**, 869 (1957).

TABLE 2

R	R′	R″	X	Formula	Required			Found			Yield %
					C	H	N	C	H	N	
CH_3	CH_3	C_2H_5	I	$C_8H_{17}N_2O_3I$	30·3	5·3	8·8	29·8	5·5	9·1	90
	C_2H_5	CH_3	I					30·6	5·4	9·0	82
C_2H_5	CH_3	C_2H_5	I	$C_9H_{19}N_2O_3I$	32·7	5·7	8·5	32·3	5·4	8·4	95
	C_2H_5	CH_3	I					32·8	6·2	8·4	86
n-C_3H_7	CH_3	C_2H_5	I	$C_{10}H_{21}N_2O_3I$	—	—	8·1	—	—	8·4	85
	C_2H_5	CH_3	I					—	—	8·5	92
n-C_4H_9	CH_3	C_2H_5	I	$C_{11}H_{23}N_2O_3I$	—	—	7·8	—	—	8·2	80
	C_2H_5	CH_3	I					—	—	7·9	90
n-C_5H_{11}	CH_3	C_2H_5	I	$C_{12}H_{25}N_2O_3I$	—	—	7·5	—	—	8·1	80
	C_2H_5	CH_3	I					—	—	7·9	75

TABLE 3

R′	R″	X	Formula	N		Formula	N	
			R = CH_3	Reqd.	Found	R = C_2H_5	Reqd.	Found
CH_3	C_2H_5	Br	$C_8H_{17}N_2O_3Br$	10·3	10·2	$C_9H_{19}N_2O_3Br$	9·8	9·7
C_2H_5	CH_3	Br			10·6			9·9
CH_3	n-C_3H_7	Br	$C_9H_{19}N_2O_3Br$	9·8	9·7	$C_{10}H_{21}N_2O_3Br$	9·4	9·8
n-C_3H_7	CH_3	Br			10·1			9·4
CH_3	n-C_4H_9	Br	$C_{10}H_{21}N_2O_3Br$	9·4	9·6	$C_{11}H_{23}N_2O_3Br$	9·0	9·1
n-C_4H_9	CH_3	Br			9·9			9·4

EXPERIMENTAL

1. *Reaction of* 3,5-*dialkyltetrahydro*-5-*nitro*-1,3-*oxazine* I *with methyl or ethyl iodide.* Compound I (2 g, 0·01 mole) was mixed with 0·02 mole methyl or ethyl iodide and the mixture left over night at room temp. The resulting *product* was filtered and recrystallized from methanol or ethanol. M.ps are given in Table 1, elementary analyses and yields in Table 2.

2. *Reaction of* I *with methyl, ethyl, n-propyl and n-butyl bromide.* The corresponding 1,3-oxazine I (2 g, 0·01 mole) dissolved in acetonitrile or anhydrous ethanol and mixed with 0·1 mole methyl bromide, in tightly stoppered flask was left at room temp for a few days. The resulting *quaternary salt*, obtained after evaporation of the solvent was recrystallized from anhydrous ethanol. The reaction of I with other alkyl bromides (used in excess) was carried out as follows: I (1 g) and 15 g alkyl bromide were boiled for 5–15 hr and the product crystallized from ethanol. The yields from 50–70%, and m.ps are given in Table 1, elementary analyses in Table 3. The identity of the quaternary salts obtained was determined by IR spectral analysis.

The NMR spectra were measured with Varian 4300-C Spectrometer at 60 Mc. The samples were prepared as dilute solutions in deuterium oxide. The spectra were calibrated by the usual side band technique, using the water peak as the internal reference.